

Representation of internal models of action in the autistic brain

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Children with autism spectrum disorder (ASD) have deficits in motor control, imitation and social function. Does a dysfunction in the neural basis of representing internal models of action contribute to these problems? We measured patterns of generalization as children learned to control a novel tool and found that the autistic brain built a stronger than normal association between self-generated motor commands and proprioceptive feedback; furthermore, the greater the reliance on proprioception, the greater the child's impairments in social function and imitation.

Theory suggests that when the brain learns to perform a movement, it builds an association between motor commands and sensory feedback. These internal models allow the brain to predict the sensory consequences of self-generated motor commands and to produce motor commands that maximize expected rewards at a minimum effort¹. Children with autism have impairments in motor control² and imitation³. Is there a fundamental difference in how these children build associations between their motor commands and sensory feedback?

Generalization is a signature of the activation fields of neurons with which the brain forms an internal model⁴. To quantify the representation of internal models in the autistic brain, we measured patterns of generalization as autistic children learned to control a novel tool. We asked 14 children with ASD (age, 10.5 ± 1.7 years) and 13 typically developing children (age, 10.4 ± 1.8 years) to play a game in which they held a robotic arm in their hand and reached with it to capture animals that had escaped from a zoo (see **Supplementary Methods**). The robot perturbed the children's arm movements by producing a force field and the children learned to control the tool so as to capture the animals. In this task, the typically developing brain builds an association between self-generated motor commands and the sensory consequences (visual and proprioceptive). The strength of each association can be inferred by how the brain generalizes the learning from the trained movements to novel movements. The training took place in the left workspace (target 1; **Fig. 1a**) while a velocity-dependent field pushed their hand perpendicular to the direction of motion. We quantified generalization in the right workspace in the intrinsic coordinates of the arm (target 3, identical joint rotations as compared to target 1), and in the extrinsic coordinates of the task (target 2, identical hand motion as compared to target 1). Movements to targets 2 and 3 were always made in

'error-clamp' trials, in which the robot produced a channel that artificially eliminated movement errors, but allowed us to measure force output at the hand.

In the baseline period in which no perturbations were present, both ASD and typically developing groups produced straight reaching movements (**Fig. 1b**). On presentation of the field, hand trajectory was perturbed (**Fig. 1b**) and the lateral deviations declined with training (**Fig. 1c**), indicating comparable learning rates ($F_{1,979} = 1.8$, $P = 0.20$). In randomly selected trials, an error clamp was presented. We quantified the amount of adaptation/generalization on each error-clamp trial by computing the ratio of the peak lateral force produced by the child and the ideal force required for compensation on that trial (**Fig. 1d**). The three targets were presented randomly. For target 1, 6 out of 96 trials were error clamp, whereas all trials were error clamp for the other targets. Therefore, for targets 2 and 3, the children were never trained in a force field and never experienced error. This design allowed us to simultaneously assay learning and generalization.

We plotted the adaptation index for each target direction during the error-clamp trials (**Fig. 1d**). The average of the first five trials in the test block was used as a measure of generalization (**Fig. 1e**). Superficially, learning appeared to be normal in children with ASD; the performance for target 1 was indistinguishable from that of typically developing children on both the last trial of learning ($P = 0.18$) and the test trials ($P = 0.94$). However, the generalization patterns were markedly different ($F_{1,25} = 15$, $P < 0.001$, interaction between group and target direction). Typically developing children generalized to the right workspace both in intrinsic ($P < 0.001$) and extrinsic ($P = 0.003$) coordinates, whereas children with ASD generalized in intrinsic coordinates ($P < 0.0001$), but not in extrinsic coordinates ($P = 0.30$). Furthermore, children with ASD generalized about twice as strong as typically developing children in intrinsic coordinates (Bonferroni *post hoc t* test, $P = 0.0017$), reflecting a much stronger than normal association between motor commands and proprioceptive feedback⁵.

In this task, the neurons that participate in representing the internal model include cells in the primary motor cortex (M1)⁶ and the premotor cortex⁷. These cells have distinct activation fields and axonal connectivity. The activation fields of M1 cells tend to be in the intrinsic coordinates of joints and muscles⁸ and these cells are strongly connected to the adjacent somatosensory cortex. In contrast, the activation fields of premotor cells tend to be in the extrinsic coordinates of the task⁹ and the cells have dense, long-range connections to the posterior parietal cortex. In the brains of typically developing children, reach adaptation produced generalization in both coordinate systems, which is consistent with a representation that engaged both the short-range connections of the primary motor/somatosensory regions and the long-range connections of the premotor/posterior parietal regions. In the brains of children with ASD, however, there is an overgrowth of localized cortical connections¹⁰ with increased white matter volume in

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Received 17 April; accepted 2 June; published online 5 July 2009; doi:10.1038/nn.2356

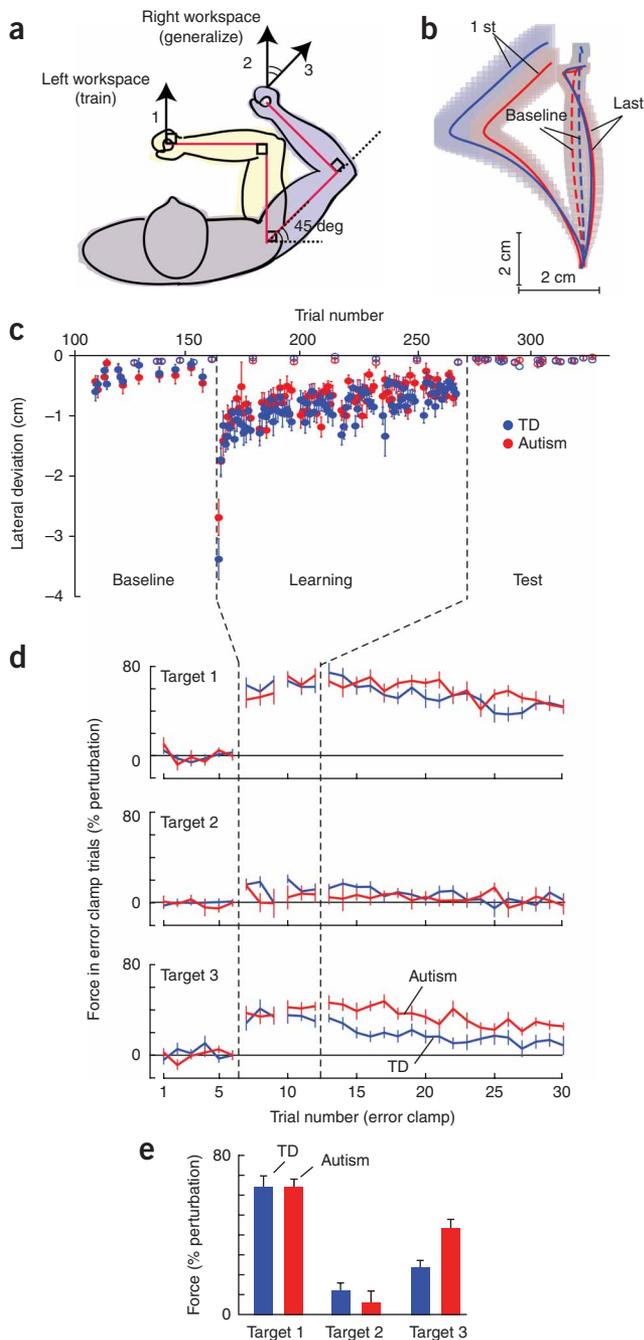


Figure 1 Learning and generalization of an internal model in typically developing children and children with ASD. **(a)** Children held the handle of a robotic arm and played a game in which the objective was to capture animals that had escaped from a zoo. At the start of the trial, the robot moved the child's arm to a starting posture. Next, an animal would appear at the target location (8 cm). If the child could reach the target in time (0.5 ± 0.05 s), the animal would be captured and the child was given points that could later be traded in for a prize. The robot produced a velocity-dependent curl force field. Learning took place in the left posture (1) and generalization was quantified in the right posture (2, identical hand motion as 1; 3, identical joint motion as 1). The target sequence was random. This study was approved by the Johns Hopkins Medicine Institutional Review Board. Informed written consent was obtained from a parent/guardian and written assent was obtained from the children. **(b)** Across subject mean \pm s.e.m. hand paths during the last trial of the baseline block and the first and last trials of the learning block. Red lines represent children with ASD. **(c)** Movement error mean \pm s.e.m. for target 1, as quantified by maximum lateral hand deviation; negative values indicate hand deviations to the left. The filled circles indicate trials in which the robot perturbed the hand and the unfilled circles indicate error-clamp trials. TD, typically developing children. **(d)** In error-clamp trials, the robot produced a channel from the start position to the target, essentially eliminating movement errors. We measured the force that the child produced against the channel walls. **(e)** The average of force in the first five error-clamp trials in the test block.

internal models that place a greater than normal reliance on proprioception, while discounting visual consequences, might place the observer at a substantial disadvantage in understanding other people's actions and imitating their movements. To test our hypothesis, we looked for correlations between how the children represented our simple reaching task and clinical measures of motor, imitation and social function.

We found that the greater the proprioceptive-driven generalization in our task, the greater the impairments in general motor function, social interaction and imitation/praxis. For example, the Autism Diagnostic Observation Schedule G (ADOS-G) Module 3 Reciprocal Social Interaction score, a standardized interview/observational assessment of social, communicative and stereotyped behaviors in children with ASD, showed that the greater the proprioceptive generalization, the greater the impairment in social function ($R = 0.572$, $P = 0.032$; **Fig. 2a**). The Total T Score from the Social Responsiveness survey, a questionnaire that is administered to the parents and inquires about the child's social interactions in naturalistic settings, was similarly correlated with proprioceptive generalization ($R = 0.586$, $P = 0.003$; **Fig. 2b**). We also found that the greater the proprioceptive-driven generalization, the greater the impairment in clinical measures of basic motor skill function ($R = 0.577$, $P = 0.004$), as measured using the total score from the Revised Physical and Neurological Examination of Subtle Signs.

We next asked whether the patterns of generalization were related to the ability of the children to imitate movements (**Supplementary Table 1**). Imitation was quantified by asking the children to reproduce movements of an examiner¹⁴, some of which were meaningful gestures (pretending to use a key in a lock) and others of which were nonmeaningful (tapping of right hand on the left forearm three times). The exam was videotaped and analyzed to score each trial as correct or incorrect. As expected, children with ASD were impaired in imitation as compared with typically developing children ($P < 0.01$). However, the greater the internal model's relative reliance on the intrinsic coordinates of movements (generalization to target 3 minus target 2), the greater the impairment in imitation ($R = -0.57$, $P = 0.006$; **Fig. 2c**).

Finally, we asked whether the patterns of generalization were also related to the ability of the children to perform skilled movements in

M1 that predicts motor impairment¹¹. Our results here suggest that one consequence of this anatomical miswiring in the brains of children with ASD is a representation of internal models that place an unusually strong reliance on proprioception.

When we observe another person performing a movement, the internal models to execute the same movement may also be activated in our brain¹². A strong prediction of this idea is that if the person that we are watching makes errors, those errors should help to teach our own internal model. Indeed, after volunteers observe another person reach while holding a robot that is producing a force field, they perform better than naive volunteers if they are tested on the same field¹³. This is consistent with the hypothesis that observation of an action instantiates the same internal models that are required for production of that action. However, because this instantiation relies on visual cues,

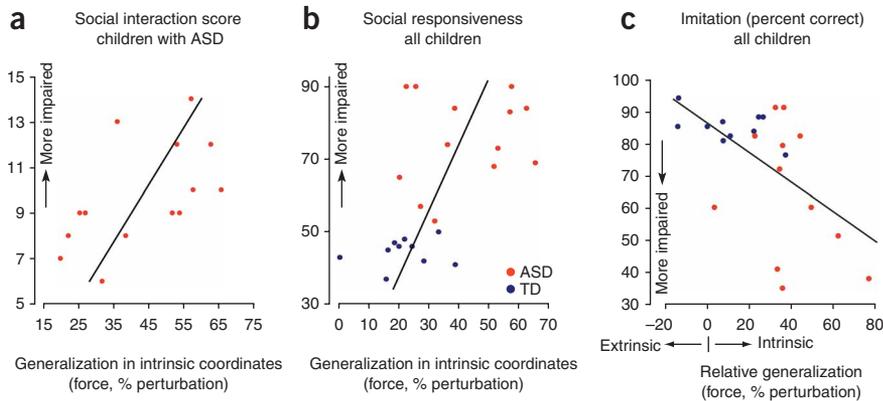


Figure 2 Motor generalization patterns as a predictor of social and imitation abilities.

(a) The ADOS-G is a standardized interview and observational assessment of social, communicative and stereotyped behaviors used for diagnosis of autism. The x axis represents the force produced for T3. (b) The Social Responsiveness Scale, a measure of social anxiety/avoidance in naturalistic settings, was scored for most of the typically developing children (10 of 13) and children with ASD (13 of 14). (c) Imitation was measured by asking the child to reproduce a sequence of 36 actions (performed one at a time), some of which were meaningful and others of which were meaningless¹⁴. The x axis represents the force produced during the test of generalization (T3 minus T2).

response to verbal commands and with common tools (that is, praxis)¹⁴. Gestures to command were assessed by verbally asking the child to perform transitive (“Show me how you brush your teeth”) and intransitive (“Show me how you salute”) actions. Tool use was assessed by giving the child a tool (for example, a comb) and asking her/him to demonstrate how to use it. Consistent with previous findings^{14,15}, children with ASD were impaired in performance of gestures to command ($P < 0.01$) and tool use ($P < 0.01$). Furthermore, the greater the internal model’s relative reliance on the intrinsic coordinates of movements (generalization to target 3 minus target 2), the greater the impairment in the ability to perform gestures to command ($R = -0.544$, $P = 0.009$) and to use common tools ($R = -0.551$, $P = 0.008$).

Our findings demonstrate that when children with ASD learn a motor task, the internal models that they form create a stronger than normal association between the self-generated motor commands and proprioception. This suggests a greater than normal dependence on cortical regions in which movements are represented in intrinsic coordinates of motion (M1 and somatosensory cortex) and a less than normal dependence on regions in which movements are represented in extrinsic coordinates (premotor and posterior parietal). A stronger than normal association between motor commands and proprioceptive feedback may be a consequence of the fact that M1 and somatosensory cortex are nearby cortical regions and short-range cortical connections are overexpressed in children with ASD¹⁰.

Note: Supplementary information is available on the Nature Neuroscience website.

ACKNOWLEDGMENTS

This research was funded by grants from the National Alliance for Autism Research/Autism Speaks, the US National Institutes of Health (R01 NS037422, R01 NS048527 and K02 NS044850) and the Johns Hopkins University School of Medicine Institute for Clinical and Translational Research, a US National Institutes of Health/National Center for Research Resources Clinical and Transitional Science Award Program (UL1-RR025005).

AUTHOR CONTRIBUTIONS

C.C.H. and J.I. conducted the robot experiments, L.R.D. conducted the social, praxis and imitation experiments and R.S. and S.H.M. wrote the manuscript.

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